General

Guideline Title

Multiple myeloma.

Bibliographic Source(s)

Alberta Provincial Hematology Tumour Team. Multiple myeloma. Edmonton (Alberta): CancerControl Alberta; 2013 Nov. 54 p. (Clinical practice guideline; no. LYHE-003). [104 references]

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- November 6, 2013 – Low Molecular Weight Heparins : The U.S. Food and Drug Administration (FDA) is recommending that health care professionals carefully consider the timing of spinal catheter placement and removal in patients taking anticoagulant drugs, such as enoxaparin, and delay dosing of anticoagulant medications for some time interval after catheter removal to decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections, including epidural procedures and lumbar punctures. These new timing recommendations, which can decrease the risk of epidural or spinal hematoma, will be added to the labels of anticoagulant drugs known as low molecular weight heparins, including Lovenox and generic enoxaparin products and similar products.

Recommendations

Major Recommendations

Monoclonal Gammopathy of Undetermined Significance (MGUS)

Diagnostic Criteria

- M-protein in serum <30 g/L

- Bone marrow clonal plasma cells (PC) <10%
- No calcium, renal insufficiency, anemia, or bone damage (CRAB) or myeloma-related organ or tissue impairment (ROTI):
  - Calcium (Ca) (corrected) >0.25 mmol/L upper limit of normal or >2.75 mmol/L
  - Renal impairment: creatinine >176 µmol/L
  - Anemia: hemoglobin (Hgb) <100 g/L or 20 g/L below lower limit of normal
  - Bone lesions: lytic lesions or osteoporosis with compression fractures
  - Others: symptomatic hyper-viscosity, amyloidosis, recurrent bacterial infections (>2/year)

The incidence of MGUS is 1% for patients over the age of 50 years, and approximately 3% for patients over the age of 70 years.

Prognosis

- Actuarial rate of progression to multiple myeloma or other lymphoproliferative disorder:
  - 17% at 10 years, 34% at 20 years, and 39% at 25 years
  - Approximately 1.5% per year
- Three risk factors for progression to multiple myeloma:
  1. Non-immunoglobulin G (IgG) monoclonal protein
  2. Serum M-protein >15 g/L
  3. Abnormal free light-chain (FLC) ratio (FLC ratio: <0.26 or >1.65)
- Risk of progression at 20 years based on number of risk factors:

• High	3/3:	58%
• High-Intermediate	2/3:	37%
• Low-Intermediate	1/3:	21%
• Low risk	0/3:	5%

- Cumulative annual rate of progression-based on FLC ratio:

• Normal FLC ratio (0.26–1.65) vs. Abnormal:	0.6% vs. 1.8%
• FLC ratio 0.25–4:	0.8%
• FLC ratio 0.125–0.25 or 4–8:	2%
• FLC ratio <0.125 or >8:	3%

Investigation and Management

Patients with MGUS do not require any treatment unless they have evidence of organ or tissue impairment (i.e., CRAB or ROTI) and thus should be classified as symptomatic myeloma rather than MGUS. Patients with MGUS are at risk to develop lymphoproliferative diseases such as myeloma, amyloidosis or malignant lymphomas. They should be re-examined annually.

At *diagnosis* the following tests should be completed:

- Complete blood count (CBC)
- Creatinine
- Ca
- Total protein
- Albumin
- Quantitative immunoglobulin levels (IgG, immunoglobulin A [IgA], immunoglobulin M [IgM])
- Serum and urine (24-hour collection) protein electrophoresis
- FLC studies
- Bone marrow aspirate and biopsy
- Skeletal survey

The following tests should be obtained *yearly* thereafter:

- CBC
- Serum creatinine
- Ca, serum, and 24-hr urine protein electrophoresis (UPEP)
- Quantitative immunoglobulins
- FLCs
- Skeletal survey

Smouldering (Asymptomatic) Myeloma

Diagnostic Criteria

- M-protein in serum ≥30g/L, and/or
- Bone marrow plasmacytosis ≥10%
- No CRAB or ROTI

Prognosis

For the purpose of predicting progression to symptomatic myeloma, smoldering myeloma can be divided into 3 risk groups:

- High-risk: serum M-protein ≥30 g/L and bone marrow PC ≥10%
- Intermediate-risk: serum M-protein <30 g/L and bone marrow PC ≥10%
- Low-risk: serum M-protein ≥30 g/L and bone marrow PC <10%

The serum FLC ratio can be used to further define the risk of progression for those with high- or intermediate-risk disease.

	Overall	High	Intermediate	Low
Median time to progression	5.5 years	2.4 years	9.2 years	19 years
Rate of progression @ 10 years	62%	76%	59%	32%
FLC ratio 0.125–8.0		59%	58%	32%
FLC ratio <0.125 or >8.0		84%	69%	33%

Treatment

No treatment is required unless progression to multiple myeloma or other lymphoproliferative disorder. Patients should be followed every 3 to 4 months and monitored for "myeloma-related" symptoms (CRAB) or organ damage.

Multiple Myeloma

Diagnostic Criteria

M-protein in serum and/or urine as detected by serum protein electrophoresis (SPEP), UPEP, or FLC
Clonal bone marrow PC or plasmacytoma
Presence of organ dysfunction: CRAB (Ca >2.75 mmol/L, creatinine >176 µmol/L, Hgb <100 g/L, bone lesions, or osteopenia with compression fractures) or ROTI

Staging

The Alberta Provincial Hematology Tumour Team as the standard staging system has adopted the International Staging System, rather than Durie-Salmon, for myeloma patients (see Tables 1 and 2 in the original guideline document).

Initial Investigations

- History and physical exam
- CBC, albumin, total protein, creatinine, β2-microglobulin, lactate dehydrogenase (LDH), calcium, alkaline phosphatase (ALP), alanine aminotransferase (ALT), bilirubin (bili)

- SPEP with immunofixation (IFE)
- 24-hr UPEP with quantification of M-protein and IFE
- Quantitative immunoglobulins (IgG, IgA, IgM)
- FLC studies (κ, λ and FLC ratio)
- Bone survey of the axial and appendicular skeleton (computed tomography [CT] scan, magnetic resonance imaging [MRI], and/or positron emission tomography [PET] scan are occasionally required for accurate measurements of plasmacytomas)
- Bone marrow aspirate and biopsy including flow cytometry
- Cytogenetics (tests in bold font are required and strongly recommended at diagnosis):
    - Fluorescence *in situ* Hybridization (FISH) for:
        - t(14;16)
        - t(4;14)
        - Deletion 17 (17p-)
        - 1q21 amplification; t(14;20) (not available through Calgary Lab Services)
    - Conventional band karyotyping at diagnosis. To indicate ploidy status and presence of del13q. Full karyotyping not required.
- MRI may be indicated in special circumstances (i.e., to rule out cord compression, central nervous system [CNS] involvement, non-secretory multiple myeloma and solitary bone or soft tissue plasmacytoma).
- PET scan is not currently indicated for the diagnosis or follow-up of multiple myeloma patients.
- Echocardiogram or cardiac MRI is only indicated if there is clinical suspicion of cardiac amyloidosis.

Myeloma-associated amyloid light-chain (AL) amyloidosis is reported in 12% to 30% of multiple myeloma patients. These patients typically fulfill the diagnostic criteria for multiple myeloma and have evidence of AL deposition confirmed by Congo red staining. The presence of AL amyloidosis should be suspected in the presence of nephrotic range proteinuria with predominant albuminuria; non-hypertensive congestive heart failure without coronary artery disease; low voltage, bradycardia or atrio-ventricular (AV) block on electrocardiogram (EKG), organomegaly, autonomic neuropathy, and carpal tunnel syndrome.

The following investigations should be ordered if the diagnosis of myeloma-associated AL amyloidosis is suspected in order to confirm the diagnosis:

- Congo red staining of the bone marrow
- Fat pad aspirate and Congo red staining if bone marrow is negative
- Direct biopsy of suspected involved organ if Congo red stain is negative in bone marrow and fat pad
- Congo red positive biopsies should be forwarded for mass spectroscopy analysis and typing

Patients with biopsy-proven amyloidosis should be classified as "Myeloma with Documented Amyloidosis" if they have ≥10% plasma cells and/or myeloma-related bone disease. For the management of these patients, please refer to "Amyloidosis" below.

Prognosis

Prognostic information reflects the treatment received during the era of a specific publication and may not reflect improvements in outcome expected with the introduction of novel agents, triple induction therapy, maintenance, consolidation, etc. (refer to Tables 3 and 4 in the original guideline document for statistics on survival outcomes).

Flow Cytometry

Flow cytometry should be performed on bone marrow biopsies at diagnosis, and on subsequent biopsies in order to confirm complete remission. The presence or absence of immunophenotyic evidence of clonal plasma cells on bone marrow samples following therapy is a strong predictor of progression-free survival (PFS) and survival.

Treatment Guidelines for Newly Diagnosed Multiple Myeloma

Goals of Therapy

The goals of therapy for young patients with multiple myeloma is to achieve the deepest possible response, ideally a complete remission, and to then maintain that response for as long as possible.

For elderly patients, the goal of therapy is to minimize symptoms and maximize response with as little toxicity as possible.

These guidelines identify effective, evidence-based treatment regimens (as opposed to single agents) to be utilized. These treatment regimens can include multi-drug and multi-step approaches, radiation therapy, or single agents when appropriate.

Patients ≤65 Years Old and Transplant-Eligible

Whenever possible, patients should be considered for a clinical trial. In the absence of a suitable trial, patients who are 65 years old or younger and are transplant-eligible, induction with a 3-drug regimen that includes a novel agent, followed by autologous stem cell transplantation (ASCT), is standard initial therapy.

For information about specific induction regimens, including bortezomib-based, thalidomide-based, and lenalidomide-based regimens; stem cell transplantation; and post-transplant therapy, see the original guideline document.

Summary

Regimens containing bortezomib and dexamethasone as well as a third agent (cyclophosphamide, lenalidomide) are the standard induction regimen prior to stem cell transplantation for transplant eligible patients with standard-risk or high-risk myeloma requiring treatment. Vincristine-doxorubicin-dexamethasone (VAD) or single-agent dexamethasone should not be used.

- Cyclophosphamide-bortezomib-dexamethasone (CYBORD) is the recommended regimen for initial therapy of newly diagnosed transplant eligible patients. Patients should receive 4–6 cycles prior to stem cell collection. Cycles are repeated every 28 days. A twice-weekly schedule can be used for sicker patients requiring a more rapid initial response to therapy.
- High-risk patients (17p deletion, t(4;14)) should be considered for initial therapy with a combination of bortezomib-lenalidomide-dexamethasone (VRD).
- Patients refractory to bortezomib, cyclophosphamide, dexamethasone (VCD; fail to achieve at least partial response [PR]) should be switched to second line therapy with lenalidomide and dexamethasone or VRD (bortezomib days 1, 4, 8, and 11, lenalidomide days 1–14, weekly dexamethasone) for several cycles prior to stem cell mobilization.
- Cyclophosphamide 2.5 G/m^2 followed by growth factor administration is used for stem cell collection.
- The standard stem cell transplant regimen consists of a single transplant conditioned with high-dose (200 mg/m^2) melphalan
- Following transplant:
    - Standard-risk patients achieving very good partial response (VGPR) or better should receive lenalidomide (25 mg daily for 21/28 days) plus dexamethasone (40 mg weekly) for 3 months followed by lenalidomide (10 mg daily) for 2 years.
    - Standard-risk patients who fail to achieve VGPR post-transplant should receive 2–4 cycles of VRD followed by lenalidomide (10 mg) daily for 2 years.
    - High-risk patients should receive 2–4 cycles of VRD followed by lenalidomide (10 mg daily) for 2 years. Patients with 17p deletion should also receive bortezomib (1.3 mg/m^2) every 2 weeks for 2 years.

Patients >65 Years Old or Transplant Ineligible

Whenever possible, patients should be considered for a clinical trial. In the absence of a suitable trial, combinations of melphalan and prednisone with novel agents (thalidomide, lenalidomide, or bortezomib) have been shown to be superior to melphalan and prednisone alone as initial therapy for transplant ineligible patients. The standard therapy for these patients should therefore include a novel agent, alkylator, and steroids. However, in frail patients, and those with significant co-morbidities or advanced age (>75 years), there is an increased risk of toxicities. For these patients, consideration should be given to dose reductions of the initial regimen, and/or the use of 2-drug combinations such as lenalidomide and dexamethasone (RD) or bortezomib and dexamethasone (VD).

For information about specific induction regimens, including thalidomide-based, bortezomib-based, and lenalidomide-based regimens, see the original guideline document.

Summary

- CYBORD for 6–12 cycles is the recommended therapy for newly-diagnosed, transplant-ineligible patients.
- Alternatively, patients may be treated with bortezomib, melphalan, and prednisone (VMP) for 6 cycles.
- Following initial therapy, all patients should receive maintenance with bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 every 3 months plus prednisone 50 mg every other day (VP).

Treatment Guidelines for Relapsed and Refractory Multiple Myeloma

Whenever possible, patients with relapsed multiple myeloma should be considered for a clinical trial. In the absence of a suitable trial, treatment of relapsed disease should be determined on individual basis depending on timing of relapse, age, prior therapy, bone marrow function, co-morbidities, and patient preference.

Autologous Stem Cell Transplant

A second high-dose chemotherapy treatment with autologous stem cell transplantation for those patients who have had a disease free interval of >2 years following their initial high-dose therapy is a reasonable consideration. The median time to progression after a salvage second autologous stem cell transplant is typically less than 1 year and the transplant-related mortality (TRM) varies between 4% and 14%. When a patient with relapsed myeloma is being considered for a salvage second transplant, the TRM and the activity of novel agents should be clearly discussed and reviewed with the patient.

Novel Drugs

- Several classes of drugs such as immunomodulatory drugs (IMIDs) (thalidomide, lenalidomide, pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib), either as single agents or combination with other drugs (dexamethasone, prednisone, melphalan, cyclophosphamide), have been shown to be active in the treatment of relapsed and refractory myeloma. Table 10 in Appendix A in the original guideline document summarizes the results of randomized phase III trials in relapsed and refractory myeloma.
- The choice of the first line of salvage therapy is mostly guided by the preference of the patient and the treating physician with a particular consideration made for enrolment into a clinical trial. The following guidelines however should be taken into account when a salvage therapy is considered:
    1. Renal failure: Lenalidomide dose adjustment is required for patients in renal failure or on hemodialysis in order to minimize the risk of cytopenia. No such adjustment is required for bortezomib.
    2. Peripheral neuropathy: Bortezomib is clearly neurotoxic and should not be the first choice of salvage therapy in patients with grade 2 sensory neuropathy or grade 1 with pain.
    3. Prior exposure to thalidomide: Prior exposure to thalidomide does not preclude patients from responding to lenalidomide. While a shorter time to progression (TTP) was reported in the MM009 and MM010 studies in patients previously exposed to thalidomide, their modified TTP (mTTP) was 8.6 months.
    4. Prior history of deep vein thrombosis (DVT): IMIDs are known to have a prothrombotic effect. Risk of thrombosis with thalidomide and lenalidomide varies between 10% and 15% and can be as high as 25% when these drugs are used with erythropoietin. Prophylaxis of DVT with aspirin or therapeutic Coumadin or low-molecular-weight heparin (LMWH) is mandatory. Bortezomib is the agent of choice over IMIDs for patients with prior life-threatening thrombotic events. If IMIDs are to be used, patients should receive prophylactic LMWH.
    5. Distance from hospital: IMIDs offer the advantage of being orally administered and therefore require less frequent visits to the hospital. Nevertheless, in non-compliant patients bortezomib is preferable.

Assessment of Response to Therapy

The response criteria and disease progression/relapse criteria of the International Myeloma Working Group, shown in Tables 7 and 8 in the original guideline document, have been adopted to assess response to therapy, progression, and other survival parameters.

As part of response assessment, all patients should have a repeat bone marrow aspirate at the time of maximum response.

Follow-up after Treatment

Myeloma patients should not be discharged from the Cancer Centre as they are rarely cured of their disease. Patients should be seen at intervals varying from 1 to 3 months depending on their disease status, and whether they are receiving monthly pamidronate. Each visit should include:

- A clinical assessment
- CBC, electrophoresis, creatinine, Ca, albumin, total protein, quantitative immunoglobulins, and measurement of M-protein (SPEP and UPEP)
- FLC studies are also required in patients with non-measurable disease, oligo-secretory and light-chain disease.
- IFE on SPEP and UPEP and bone marrow biopsy are required to confirm complete response (CR).
- FLC is required to confirm stringent CR (sCR).
- A skeletal survey should be obtained once per year.

The recommended follow-up plan as outlined by the International Response Criteria includes:

- Patients undergoing therapy should be tracked monthly for the first year of new therapy and every other month thereafter.
- Patients with "measurable disease" need to be followed by both SPEP and UPEP for response assessment and categorization.
- Except for assessment of CR, patients with measurable disease restricted to the SPEP will need to be followed only by SPEP; correspondingly, patients with measurable disease restricted to the UPEP will need to be followed only by UPEP.

- Patients with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these two tests and not by the FLC assay. FLC response criteria are only applicable to patients without measurable disease in the serum or urine, and to fulfill the requirements of the category of sCR.
- To be considered CR, both serum and urine IFE must be carried out and be negative regardless of the size of baseline M-protein in the serum or urine; patients with negative UPEP values pre-treatment still require UPEP testing to confirm CR and exclude light-chain or Bence-Jones escape.
- A skeletal survey is not required for assessment of response unless clinically indicated, but is recommended once a year in clinical practice.
- Bone marrow is required for categorization of CR, and for patients with non-secretory disease. Bone marrow aspirate should be performed at the time of maximum response to therapy.

For information about supportive therapy, including bisphosphonates, osteonecrosis of the jaw (ONJ), and percutaneous vertebral augmentation or kyphoplasty, see the original guideline document.

Solitary Plasmacytoma

The location of the solitary plasmacytoma is crucial to predicting its natural history. The majority of patients with extra-osseous (non-bone-involving) plasmacytoma have localized disease which is potentially curable with irradiation. *The majority of patients with solitary plasmacytoma of bone will eventually manifest overt multiple myeloma* (>50% will progress to multiple myeloma).

Solitary Plasmacytoma of Bone

- Typically no M-protein in serum/urine (a small M-component is present in 50%)
- Single area of bone destruction due to clonal PC
- Bone marrow not consistent with multiple myeloma
- Normal skeletal survey (and MRI of spine and pelvis if done)
- No CRAB or ROTI (no end organ damage other than solitary bone lesion)

Extramedullary Plasmacytoma

- Typically no M-protein in serum/urine (a small M-component is present in 50%)
- Extramedullary tumour of clonal PC
- Normal bone marrow
- Normal skeletal survey
- No CRAB or ROTI (no end-organ damage including bone lesions)

Staging

Patients should undergo all the usual tests for multiple myeloma. CT scan of the plasmacytoma should be obtained prior to radiation therapy. An MRI of the spine and pelvis may show unsuspected and asymptomatic skeletal lesions. This finding would place the patient in the smoldering myeloma category. PET scan could help determine the extent of bone or soft tissue involvement.

Treatment and Prognosis

Solitary Plasmacytoma of Bone

- Treatment consists of radiation in the range of 40 Gy–50 Gy.
- Solitary plasmacytomas >5 cm, the persistence of an M-protein after radiation or evidence or marrow involvement by MRI have a greater incidence of progression.
- 50% of patients with solitary plasmacytoma are alive at 10 years.
- 25% to 40% of patients survive disease-free at 10 years.
- *Overt multiple myeloma occurs in almost 50% of patients* with solitary plasmacytoma of bone (progression may occur 15 years later).
- Recommend stem cell harvest in transplant-eligible patients.

Extramedullary Plasmacytoma

- Treatment with localized radiation (40 Gy–50 Gy) and is often curative.
- Plasmacytoma may recur locally or metastasize to regional nodes.
- *Symptomatic multiple myeloma occurs in only 15% of patients.*

Follow-up

- CBC, serum creatinine, Ca, and SPEP should be done every 3 months for 1 year, then every 6 months for 2 years, then annually.
- A 24-hr UPEP and skeletal survey should be done annually, for at least 5 years for extra-osseous plasmacytomas, and for 5–10 years for osseous plasmacytomas.

Amyloidosis

Classification

The systemic amyloidosis can be divided into 3 major subtypes (refer to Table 12 in the original guideline document).

1. Primary (also called AL type) -- most common subtype with 90% involving lambda light chain
2. Familial transthyretin-associated (ATTR type)
3. Secondary (AA type)

Diagnostic Pathway for AL Amyloidosis

Consider AL amyloidosis in the differential if there is evidence of:

- Non-diabetic nephrotic syndrome
- Cardiomyopathy non-ischemic: echo shows "left ventricular hypertrophy (LVH)"
- Hepatomegaly with no scan defects
- Chronic inflammatory demyelinating polyneuropathy
- "Atypical myeloma" urine light-chain + and marrow <10% plasma cells

Amyloidosis remains a tissue diagnosis. Tissue biopsy, either of an involved organ or a surrogate site (e.g., abdominal fat), must demonstrate amyloid deposition by classic Congo red staining or electron microscopy. Since MGUS is not an uncommon finding, especially in patients with advanced age, the presence of a monoclonal protein in a patient with positive Congo red staining on a tissue biopsy is not adequate to make a diagnosis of AL amyloidosis. In addition, some patients with AL amyloidosis will not have an abnormal SPEP or FLC assay. Immunohistochemical staining is frequently unreliable and not able to accurately determine the type of amyloid present. Therefore laser microdissection with mass spectrometry (LMD/MS) is now the gold standard for typing amyloid, enabling precise identification of type in over 98% of cases.

Initial Tests

- CBC, creatinine with measured creatinine clearance, Ca, ALP
- Quantitative Ig, SPEP with IFE
- 24-hr urine UPEP with IFE and 24-hr urine for creatinine clearance
- Serum-FLC studies
- Serum troponin T and I and brain natriuretic peptide (pro-BNP)
- Serum β2 microglobulin
- Bone marrow biopsy with flow cytometry, Congo red staining, and FISH for t(4;14), t(14;16), and del17p
- Biopsy of subcutaneous fat or kidney, liver, or other involved organ if required for diagnosis
- Cardiac MRI and/or echocardiogram to assess left ventricle (LV) septum thickness and cardiac function
- EKG and Holter study to rule out arrhythmia if suspected
- Abdominal ultrasound (US) to assess liver and spleen
- Upper and lower endoscopy if gastrointestinal (GI) bleed or uncontrolled diarrhea or >10% weight loss related to possible malabsorption
- Skeletal survey rule out myeloma with lytic bone lesions
- Subtyping of the amyloid deposit (by mass spectrometry coupled with capture laser dissection)

Screening

- 90% will have a detectable Ig abnormality either by IFE of serum or a 24-hr urine specimen or Freelite (free light-chain).
- Screening SPEP or UPEP is inadequate as they often fail to show the presence of M-spike.
- Patients with normal serum IFE → abnormal FLC ratio is detected in 85% of kappa and 80% of lambda amyloid patients.
- Patients with normal serum and urine IFE: FLC detected a kappa protein in 86% of kappa amyloid and a lambda in 30% of lambda amyloid.
- The combination of FLC assay with serum and urine protein electrophoresis will identify a monoclonal protein in 99% of patients.
- Screening test sensitivity

- Amyloid IFE: 90%
- Amyloid stains performed on routine fat biopsy: 73%
- Amyloid stains performed on bone marrow: 72%
- As shown in Table 13 in the original guideline document, patients with AL amyloidosis might have a negative Congo red stain of their bone marrow and fat pad aspirates in 13% of cases. In this situation, a direct biopsy of the involved organ (renal, myocardium) should be considered.

Prognostic Markers

1. Echo with Doppler: septal thickness (>15 mm) and ejection fraction (EF)
2. Serum troponin T/I and N-terminal brain natriuretic peptide (NT-proBNP)
3. β2-microglobulin

Staging for Patients with Primary Amyloidosis

Clinical Staging

Threshold values: cTnT <0.035 µg/L; cTnI <0.1 µg/L and NT-proBNP <332 ng/L

- Stage I (low risk): both troponin and NT-proBNP are below the threshold
- Stage II (intermediate risk) if only one marker is below the threshold
- Stage III (high risk) if both are equal to or above the threshold

The median overall survival rates for stages I, II, and III are 27.2, 11.1, and 4.1 months respectively. Refer to Figures A and B in the original guideline document.

Definition of Organ Involvement

- Kidney: 24-hr urinary protein >0.5 g/day, predominantly albumin
- Heart: mean wall thickness >12 mm on echocardiogram, no other cardiac disease responsible for the increase in wall thickness
- Liver: total liver span >15 cm in the absence of heart failure, or ALP level >1.5 times upper limit of normal
- Nerve: symmetric sensorimotor peripheral neuropathy in the legs, gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration
- Gastrointestinal tract: symptoms and verification by means of biopsy
- Lung: symptoms and verification by means of biopsy, interstitial radiographic pattern
- Soft tissue: tongue enlargement, arthropathy, skin purpura, myopathy

Treatment Guidelines for AL Amyloidosis

Most hematological responses will result in clinical improvement of some degree even up to 12 months after the hematological responses have been recorded. The goal of the therapy is to halt the production of the amyloid protein (hematological remission, response criteria below). It should be noted that the treatment of an amyloidosis patient is multidisciplinary and requires the active involvement of a nephrologist and cardiologist.

Bortezomib-based Regimens

In the absence of grade 2 neuropathy or grade 1 neuropathy with pain, bortezomib-based regimen should be considered first line of therapy:

- The standard initial therapy for amyloidosis is CyBorD (bortezomib 1.5 mg/m^2 weekly, cyclophosphamide 300 mg/m^2 orally weekly, and dexamethasone 40 mg weekly).

Melphalan plus Dexamethasone

Treatment with melphalan and dexamethasone remains the "gold standard" therapy for AL amyloidosis. The recommended treatment regimen is melphalan 10 mg/m^2 days 1 to 4 plus high-dose oral dexamethasone (40 mg per day on days 1–4) for up to 18 treatment courses if no severe adverse effects have occurred.

Autologous Stem Cell Transplant

Only one randomized trial of autologous stem cell transplant versus melphalan plus dexamethasone was conducted and failed to show any difference in event-free survival (EFS) or overall survival (OS) between these 2 treatments. This study was however likely underpowered to detect

a difference in survival between the treatment arms. Several other non-randomized studies did report high response rates with prolonged survival compared to matched-cases treated with melphalan plus dexamethasone. Stem cell transplantation should ideally be conducted only in the setting of a clinical trial, or for highly motivated patients who do not have poor prognosis disease (severe heart disease or ≥3 organs involved) and in a center experienced with this procedure.

When stem cell transplantation is performed, the following guidelines should be followed:

- Patients should be <65 years old, have <3 major organs involved, and no congestive heart failure.
- Three risk categories according to Comenzo and Gertz are as follows:
    1. Good risk patients are of any age and have 1 to 2 organs involved, no cardiac involvement and creatinine clearance >50 mL/min.
    2. Intermediate risk patients are <71 years old and have 1 to 2 organs involved, one of which must include cardiac or renal with creatinine clearance <51 mL/min.
    3. Poor risk patients have either three organs involved or advanced cardiac involvement.
- Stem cell mobilization with granulocyte colony-stimulating factor (G-CSF) alone (5–6 μg/kg q12 hours for 5 days).
- Debulking with VAD or other regimens pre-transplant is unnecessary and not recommended.
- Conditioning with dose melphalan (140–200 mg/m^2) adjusted according to number of organ involved and the degree of heart failure.

Novel Agents (Thalidomide, Lenalidomide)

Several phase I/ II studies have been reported using one of these novel agents; however their therapeutic effect was limited by their toxicity. Table 11 in Appendix A in the original guideline document summarizes some of these studies.

Supportive Treatment

Supportive care is a fundamental part of an integrated treatment approach to AL amyloidosis patients and requires the coordinated expertise of several specialists. Table 14 in the original guideline document summarizes the recommended supportive measures.

Response Criteria and Disease Monitoring

The goal of therapy is a complete hematologic response. In patients with significant comorbidities or treatment related side effects, a 90% reduction in involved free light chains (iFLC) is likely a reasonable target. Failure to achieve a 50% reduction in the iFLC has been associated with significantly shortened survival.

Hematologic (Immunochemical) Response

- Complete response: serum and urine negative for a monoclonal protein by means of IFE, normal kappa:lambda FLC ratio, and normal absolute value of the involved serum FLC (in patients without renal insufficiency).
- Partial response: serum M component >0.5 g/dL and 50% reduction; light chain in the urine with a visible peak >100 mg/day and 50% reduction; or FLC >10 mg/dL and 50% reduction.
- Progression after complete response: any detectable monoclonal protein or abnormal FLC ratio (light chain must double).
- Progression after partial response or stable response: 50% increase in serum M-protein to >0.5 g/dL or 50% increase in urinary M-protein to >200 mg/day with a visible peak.

Organ Response

- Heart: mean interventricular septal thickness decreased by 2 mm, 20% improvement in EF, improvement by 2 New York Heart Association classes without an increase in diuretic use, and no increase in wall thickness
- Kidney: 50% decrease (a decrease of at least 0.5 g/day) in 24-hr urinary protein (must be >0.5 g/day before treatment), creatinine and creatinine clearance must not worsen by 25% over baseline level
- Liver: 50% decrease in abnormal ALP value, at least 2 cm decrease in liver size on radiographic imaging
- Nerve: improvement in nerve conduction velocity on electromyogram (rare)

Disease Monitoring

- Patients who are being actively treated should be monitored monthly for treatment-related toxicities (e.g., cytopenia, nausea). In addition, assessment of their organ involvement (e.g., heart failure, renal dysfunction, neuropathy) should be performed. Response to therapy should also be monitored on a monthly basis while actively treated, and every 8 to 10 weeks thereafter. Recommended laboratory tests include:
    - CBC, electrolytes, creatinine, ALP
    - SPEP, 24-hr UPEP, FLC studies

- In addition, EKG and echocardiogram should be assessed every 6 months. Other investigations such as nerve conduction studies and abdominal ultrasounds will need to be repeated only if there is evidence of organ involvement at baseline and for the evaluation of response to therapy.

Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Initial Therapy for Newly Diagnosed Multiple Myeloma
- Summary of Treatment Recommendations in Multiple Myeloma Patients ≤65 Years Old and Transplant Eligible

Scope

Disease/Condition(s)

Multiple myeloma, monoclonal gammopathy, smoldering myeloma, and amyloidosis

Guideline Category

Diagnosis

Evaluation

Management

Risk Assessment

Treatment

Clinical Specialty

Hematology

Medical Genetics

Oncology

Radiation Oncology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To outline the diagnostic criteria for multiple myeloma, monoclonal gammopathy, smoldering myeloma, and amyloidosis
- To describe current treatment strategies for multiple myeloma, monoclonal gammopathies, smoldering myeloma, and amyloidosis

Target Population

Adults over the age of 18 years with suspected or confirmed multiple myeloma or related disorders

Note: Different principles may apply to pediatric patients.

Interventions and Practices Considered

Diagnosis/Risk Assessment

1. Monoclonal gammopathy of undetermined significance (MGUS)
    - Assessment of M-protein in serum
    - Assessment of bone marrow clonal plasma cells (PC)
    - Assessment of calcium, renal impairment (creatinine levels), anemia (hemoglobin), bone lesions (CRAB), or myeloma-related organ or tissue impairment (ROTI)
    - Assessment of risk factors for progression (non-immunoglobulin G [IgG] monoclonal protein, serum M-protein, abnormal free light-chain [FLC] ratio)
    - Complete blood count (CBC)
    - Total protein
    - Albumin
    - Serum and urine protein electrophoresis
    - Quantitative immunoglobulins (IgG, immunoglobulin A [IgA], immunoglobulin M [IgM])
    - Skeletal survey
    - Bone marrow aspirate and biopsy including flow cytometry
2. Smouldering (asymptomatic) myeloma
    - Assessment of M-protein in serum
    - Assessment of bone marrow clonal PC
    - Assessment of CRAB or ROTI
3. Multiple myeloma
    - Assessment of M-protein in serum
    - Assessment of bone marrow PC
    - Assessment of organ dysfunction
    - International Staging System
    - Initial investigations, including history and physical exam, laboratory tests, bone survey (radiologic imaging), bone marrow aspirate and biopsy including flow cytometry, cytogenetics
4. Solitary plasmacytoma
    - Usual tests for multiple myeloma
    - Computed tomography (CT) scan
    - Magnetic resonance imaging (MRI) of the spine and pelvis
    - Positron emission tomography (PET) scan to determine the extent of bone or soft tissue involvement
5. Amyloidosis
    - Classification (primary, familial transthyretin-associated, or secondary)
    - Initial laboratory tests included tissue biopsy of an involved organ or surrogate site
    - Screening for detectable Ig abnormality
    - Prognostic markers
    - Staging
    - Investigations for amyloid light-chain (AL) amyloidosis (evidence of amyloid light-chain deposition confirmed by Congo red staining)

Treatment/Management

1. Multiple myeloma
    - Considerations for clinical trial
    - Induction regimens containing at least one novel agent (e.g., bortezomib, lenalidomide, thalidomide)
    - Cyclophosphamide, bortezomib, dexamethasone (CYBORD)
    - Lenalidomide, bortezomib, dexamethasone (VRD)

- Stem cell transplantation
- Bortezomib, melphalan, prednisone (VMP) for 6 cycles
- Second high-dose chemotherapy treatment with autologous stem cell transplantation
- Post-transplant therapy (consolidation, maintenance)
- Maintenance with bortezomib plus prednisone (VP)
- Use of novel drugs as salvage therapy
- Assessment of response to therapy using criteria of the International Myeloma Working Group
- Follow-up after treatment
- Supportive therapy (bisphosphonates, minimizing osteonecrosis of the jaw, percutaneous vertebral augmentation or kyphoplasty, radiation therapy)

2. Solitary plasmacytoma
    - Radiation therapy
    - Follow-up
3. Amyloidosis
    - Treatment with bortezomib-based regimens or melphalan plus dexamethasone
    - Autologous stem cell transplant (ASCT)
    - Novel agents (thalidomide, lenalidomide)
    - Supportive treatment
    - Response criteria (hematologic response, organ response)
    - Disease monitoring

Major Outcomes Considered

- Survival rates (5-year, overall, event-free, progression-free)
- Progression rate
- Time to progression
- Response rate
- Quality of life
- Skeletal morbidity
- Transplant-related mortality

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (patient or population, intervention, comparisons, outcomes).

Guideline Questions

- What are the diagnostic and prognostic criteria for multiple myeloma and related disorders?
- What are the most suitable management strategies of multiple myeloma and related disorders?

Search Strategy

The MEDLINE, PubMed, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews databases were searched (1966 through August, 2012). In addition, the American Society of Clinical Oncology (ASCO) and American Society of Hematology

(ASH) Abstracts and Proceedings databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Hematology Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Utilization Resource Unit (GURU).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formulating Recommendations

The working group members formulated the guideline recommendations based on the evidence synthesized by the Knowledge Management (KM) Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the Guideline Utilization Resource Unit Handbook (see the "Availability of Companion Documents" field), the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the Guideline Utilization Resource Unit (GURU) does not use formal rating schemes for describing the strength of the

recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Hematology Tumour Team.

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it will be officially endorsed by the Provincial Tumour Team Lead and the Executive Director of Provincial Tumour Programs.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and treatment of multiple myeloma, monoclonal gammopathy, smoldering myeloma, and amyloidosis

Potential Harms

- The vincristine-doxorubicin-dexamethasone (VAD) regimen should not be used to the toxicity of this regimen (neurotoxicity, cardiac toxicity, myelosuppression) and its inferior outcomes compared to bortezomib containing regimens.
- Patients who are being actively treated should be monitored monthly for treatment-related toxicities (e.g. cytopenia, nausea). In addition, assessment of their organ involvement (e.g., heart failure, renal dysfunction, neuropathy) should be performed. Response to therapy should also be monitored on a monthly basis while actively treated, and every 8 to 10 weeks thereafter.
- Randomized controlled trials of thalidomide have demonstrated higher incidence of adverse events with thalidomide as compared to

standard therapy. In particular, venous thromboembolism (VTE), peripheral neuropathy, and constipation are increased. Risk of VTE (between 4% and 20%) is greater when thalidomide is combined with steroid and/or chemotherapy but less when thalidomide used as maintenance.

- When therapy is started in elderly patients, frail patients, the very elderly (over 75 years of age) and those with significant co-morbidities are at an increased risk of toxicity from combination regimens. As a result of such toxicity, therapy is often terminated early resulting in poorer outcomes than if less intense but more tolerable therapy were to be given for a longer period of time.
- Risk of thrombosis with thalidomide and lenalidomide varies between 10% and 15% and can be as high as 25% when these drugs are used with erythropoietin.
- Lenalidomide dose adjustment is required for patients in renal failure or on hemodialysis in order to minimize the risk of cytopenia. No such adjustment is required for bortezomib.
- Bortezomib is clearly neurotoxic and should not be the first choice of salvage therapy in patients with grade 2 sensory neuropathy or grade 1 with pain.

Contraindications

Contraindications

Contraindications for Kyphoplasty in Multiple Myeloma

Absolute

- Contraindication to general or local anesthesia
- Pregnancy
- Bleeding disorder
- Active Infection
- Pain unrelated to vertebral collapse
- Cord compression
- Presence of overt Instability
- Severe cardiopulmonary insufficiency
- Allergy to contrast

Relative

- Lesions above T3
- Vertebra plana
- Fracture with obstructing plasmacytoma
- Retro-pulsed bone

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present and review the guideline during local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services Web site.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Hematology Tumour Team. Multiple myeloma. Edmonton (Alberta): CancerControl Alberta; 2013 Nov. 54 p. (Clinical practice guideline; no. LYHE-003). [104 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Nov

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

Guideline Committee

Alberta Provincial Hematology Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Hematology Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists.

Financial Disclosures/Conflicts of Interest

None of the authors of this guideline had any conflict of interest related to evidence or recommendations in this guideline.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the Alberta Health Services Web site .

Availability of Companion Documents

The following is available:

- Guideline utilization resource unit handbook. Edmonton (Alberta): CancerControl Alberta; 2013 Jan. 5 p. Electronic copies: Available from the Alberta Health Services Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 12, 2014. The information was verified by the guideline developer on September 25, 2014.

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